EMBO *reports*

interview

From bench to bedside

An interview with Alain Fischer, immunologist and gene therapist at the Necker Hospital in Paris, France

EMBO *reports* (ER): In terms of basic research, what is your area of interest?

Alain Fischer (AF): We are working on genetic diseases of the immune system that are caused by mutations in a single gene. So it's Mendelian genetics. Once we have identified a certain phenotype, we try to find the gene that is affected by the mutations. Sometimes this leads to the identification of new genes. This starts the classical biochemical approach towards understanding the function of the protein. More specifically, we are working on T-cell differentiation, B-cell function and terminal B-cell differentiation, cytotoxic T cells and lymphocyte apoptosis.

ER: How does this relate to gene therapy?

AF: One possible application of this research is to add a copy of a normal gene back into cells in which the original gene is defective. In theory, we might be able to cure the disease.

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ER: Which diseases are you trying to treat?

AF: In terms of gene therapy, we have been working on severe combined immunodeficiency (SCID). This very rare condition affects one in 100,000 live births and is characterized by the complete absence of T lymphocytes, and sometimes other cells of the immune system, as a result of multiple distinct genetic defects. So even rare diseases need to be studied individually, one by one. First you start by genotyping the patients to understand which gene is affected, then you need to understand the function of the protein—for example, in animal models—to see whether there is a feasible approach to correct the defect. But before starting clinical studies you need to understand the biochemical background: how the gene is expressed, what it does and so on.

ER: How long did it take from identifying mutations to conducting clinical trials?

AF: The gene was first cloned by a Japanese group in 1992, and the first patient was treated in 1999. Seven years is fairly fast. Gene-transfer techniques, which of course were required, were developing in parallel and we could immediately define and design the vectors. We made a knockout mouse in 1994 to understand the pathology and to see whether we could correct the immunodeficiency using gene transfer in a way that could be applied to human patients. Once we knew that we could restore T-cell development in this mouse model and in cell lines *in vitro*, we thought that we might be able to treat patients. In 1997, we applied to the French regulatory authority and, after we obtained their permission, we started treating patients in spring 1999—almost eight years ago.

ER: Which gene-transfer approach did you use for your first patients?

AF: The technology we used was *ex vivo* gene transfer into bone marrow progenitor cells. We needed to integrate the therapeutic gene into the genome because the transgene needs to be replicated through cell division in order to be expressed. In the haematopoietic system there are many cell divisions; T-lymphocyte precursors in particular divide a large number of times before they mature. At that time, the only possibility was to use retroviral vectors, which have their limitations. We understood from different studies that these vectors cannot cross the nuclear membrane. So they can't transduce cells in the G0–G1 phase like most stem cells. In terms of efficiency, this is a major limitation. Some cells are of course dividing and those cells are sensitive to integration because their nuclear membrane is dissolved transiently.

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ER: How do you achieve a balance between efficiency and safety of the vector?

AF: Of course, the more efficient the vector is, the better it is. However, SCID was a good model because we didn't need efficient gene transfer. A haematopoietic stem cell has the capacity to divide many times so that you can get billions of T lymphocytes from a single transgenic cell. If these T-cells work properly, they can express the transgene for many years because these cells are very long-lived.

In terms of efficiency, we know that the system works fairly well. We have treated ten patients and a group in the UK has treated another ten patients. The procedure has been efficient in 18 of these patients and somewhat efficient in at least one other, which is fairly good. However, in three patients we observed acute lymphoblastic leukaemia-like disease requiring chemotherapy, which turned out to be effective in two of three.

ER: If you could start all over again, which alternative approach would you choose?

AF: If I started all over again, I would like to have a system that is as efficient but safer. Once the provirus is integrated it can modify the expression of nearby genes. The expression of the transgene relied on the viral long terminal repeat (LTR), which is a potent enhancer. Such an enhancer can drive the expression not only of the transgene, but also of a nearby gene. This is harmful if this gene is an oncogene, which we have unfortunately observed in three patients. That's what we want to get rid of. At least, we want to reduce the risk of such unwanted events occurring. We can probably reduce the risk by using so-called self-inactivating vectors in which the LTR, which is needed to achieve integration, is auto-inactivated at the time of integration, leading to the loss of enhancer activity. Different groups have demonstrated that one can use such self-inactivating vectors. In principle, such vectors could significantly reduce the risk of such a complication.

ER: When will your trials continue?

AF: Today we are not treating patients. Hopefully, we will start again with new vectors in the near future in collaboration with our colleagues in London. We are preparing clinical trials for SCID, the same disease we have treated before, and other forms of the disease.

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ER: What expectations do you have for gene therapy in the future?

AF: I am not an expert in science fiction. First of all, it is absolutely clear that gene therapy is not going to be 'the' therapy. It is just one approach among many others. Of course, inherited monogenic diseases for which gene therapy is favourable—such as T-cell selection in SCID—are good candidates. But there are not so many examples for which gene therapy has worked. There are two forms of SCID—the one we have treated and another one treated by an Italian group—and there are now promising results from Michele de Luca's group in Italy for *Epidermolysis bullosa*, a genetic disorder of the skin (Mavilio F *et al* (2006) *Nat Med* **12:** 1397–1402). There are some other preliminary data, which suggest that for a few other disorders gene therapy could work one day.

There have been a lot of efforts by many groups to use gene therapy against cancer but the data are very scarce. There was a publication last year (Morgan RA *et al* (2006) *Science* **314**: 126–129) about treating melanomas with engineered T lymphocytes to fight cancer cells, with some success in two patients. We will have to see, but using gene therapy in cancer will be in combination with other approaches, certainly not alone. Gene therapy is not going to cause a revolution in medicine.

> **In medical research […] you need to take the time to discuss and explain everything openly with the parents, the scientific community and the regulatory authorities**

ER: Are there alternative approaches to retroviral gene vectors?

AF: Encapsulated DNA is a possibility, but for genetic diseases the ultimate goal is not to add a gene but to repair it, to really fix the mutation. Such an elegant approach would use homologous recombination with high frequency and sufficient specificity to target the correct piece of DNA.

ER: How many case studies of clinical gene therapy have there been so far?

AF: There have been more than 700 trials using gene therapy. The total number of patients is in the thousands or even more. The number of patients who have benefited from gene therapy is of course much lower. Around 30 patients have been treated for different forms of SCIDs. The procedure has been efficient in most of them; three have developed cancer, two of whom are alive with a functional bone marrow, whereas it was fatal for one patient. Clinical trials are not always made with the primary aim of efficiency—they also test tolerance and feasibility. So it's not fair to compare these low numbers with the overall number of patients treated by gene therapy. We provided a proof of principle and, based on that, we have to improve the technology.

ER: How did you communicate the risks of gene therapy to patients and their families?

AF: In the SCID trial that we performed, the patients were very young: one month to one year old. Despite the fact that we underestimated the risk at that time because of the state of the knowledge, we mentioned it in the documents that the parents read and explained it to them. It is not easy to explain these things to people who don't have a background in science, but we took our time and used non-technical terms. The risk was balanced by the fact that SCID is a fatal disease and leads to death within the first year of life; there is no exception. The alternative therapy—allogenic bone marrow transplantation—has a significant risk of failure. So we explained that our procedure could work better than the alternative and eventually they all accepted. We tried to explain everything in an objective way, and several people who were not directly involved in the trial described the protocol.

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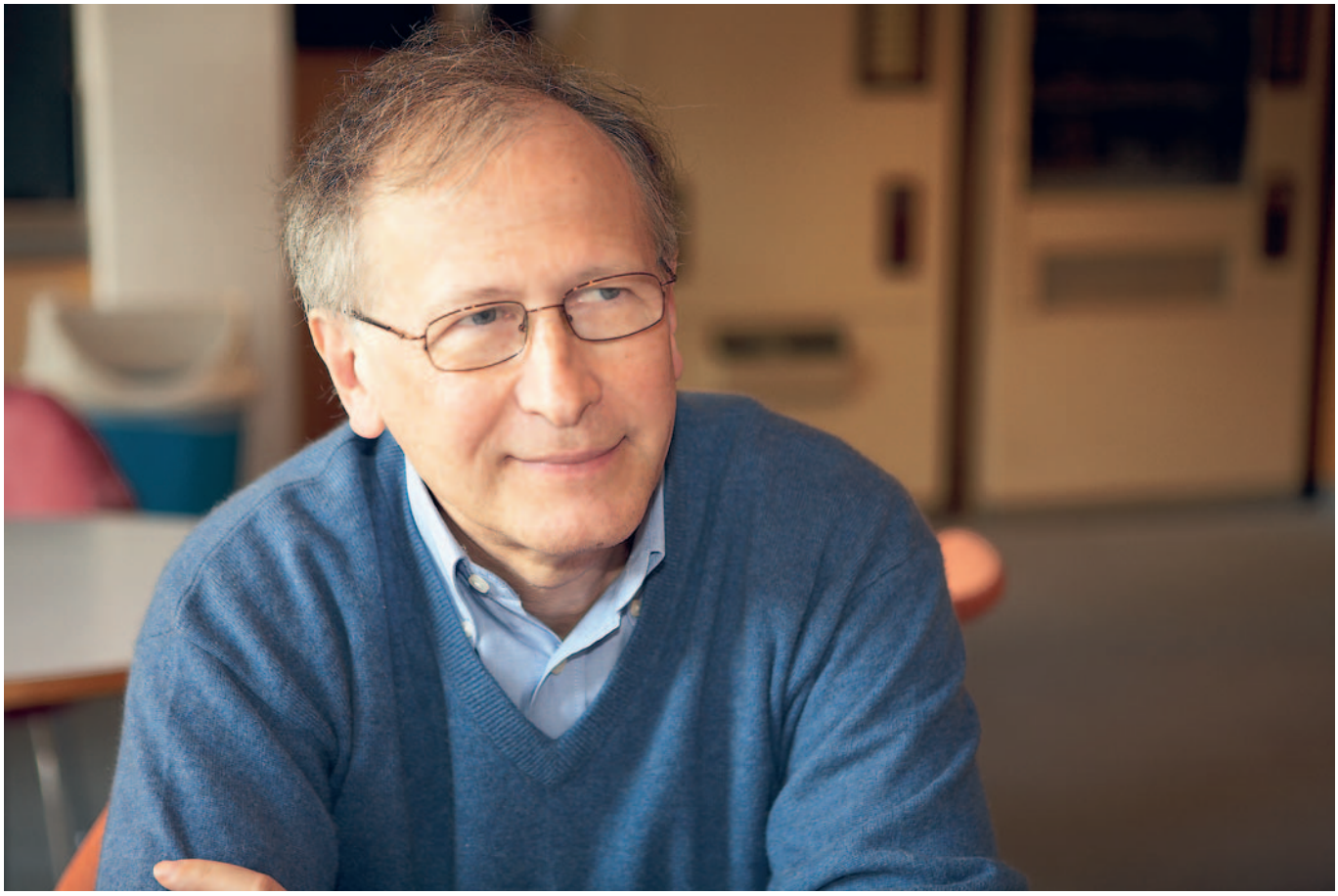
ER: What crucial decisions did you have to take during the clinical trials?

AF: The main principle is a benefit–risk assessment of our gene therapy versus the classic therapy. We thought we had enough data to show that gene therapy works better, which is indeed the case. Once we observed the first complications, we immediately knew that we had to understand what was happening, so we stopped enrolling more patients. Of course we were in touch with the regulatory authorities. Actually they took the same position: to stop there and to understand what was going on. In medical research you sometimes have to face both anticipated and unanticipated problems. This is not always easy because there are human lives involved. Practically speaking, it means that you need to take the time to discuss and explain everything openly with the parents, the scientific community and the regulatory authorities.



ER: Were you personally involved in that?

AF: It was my responsibility, but I did this together with other people. If you believe in a medical project, you have to deal with all aspects of it. This was not always easy, for instance when we considered that we had to inform everyone in the world working on that field of gene therapy about the side effects, including the regulatory authorities. We decided we had to pass on the information immediately but we asked everyone not to make the information public before we had informed the families of the patients. We did not want them to learn it from the media. It worked everywhere in Europe but not in the USA, where we had a very difficult time with one of the regulatory authorities. They demanded that we make the information public. I said I had to talk to the patients' families, who came from different European countries and could not be contacted and informed within one day. But the authorities did not want to listen. That was very unpleasant. I approached the ministry of health in Paris to help me to convince the Recombinant DNA Advisory Committee of the US National Institutes of Health (NIH) to wait one week. There was absolutely no way I could do that, which upset me very much. I had to call all the families in one night and inform them by telephone that there was a problem, and that it was going to be made public the next day in the USA. It was really unpleasant.

ER: How did the media coverage affect your work?

AF: Generally speaking, the relationship between science and the media is not so difficult. The media is what it is—not always very accurate. They like anything that is sensational. They sometimes have difficulties putting things in the right perspective. It's always easy to criticize journalists and the media, but I think the responsibility is also on scientists. There are numerous examples of scientists, especially doctors of medicine, who have made claims that were really out of proportion with their findings. The media are no experts, by definition.

ER: Did this experience change you?

AF: Most of the time scientists don't want to communicate. Or they communicate with reservation. First and foremost, I believe there is no reason not to say something. I always tried to control my comments to some extent, and talk through our research agencies. Now I know the system better. I know the people I can trust, and those I can't. It's important that we as scientists communicate, especially in times when science is not in very good shape in the Western world. But we have to communicate in a timely and correct way. And this is very difficult. It is hard to say what I would do better now compared with seven years ago. There are people I will never talk to again, and people I am keen to talk to because I know that they can be trusted

and are reasonable, and will transmit the right information.

ER: How did you integrate the knowledge of gene transfer early into the project?

AF: Of course the knowledge of gene transfer was not there from the beginning. We had a good background in immunology and we had a reasonable background in genetics but not in gene transfer. We contacted Olivier Danos and Jean-Michel Heard at the Institut Pasteur in Paris, and Richard Mulligan at Harvard Medical School in Cambridge, MA, USA, who had experience in gene transfer. They helped us and provided us with vector backbones, and then we learned. Today, with Marina Cavazzana-Calvo, we have an expert team.

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ER: Your work fuses medical practice and basic research. How do you integrate molecular research into your clinical work?

AF: I am still working as an MD with children with genetic disorders of the immune system. The research we are doing with these patients has two objectives. First, if we can understand the mechanism of a disease, we can develop new tools for diagnosis, better understand what is going on in patients, define better ways of prognosis and maybe develop new therapeutics. The second objective is to use these diseases as a model to study how the immune system works, which brings us back to basic science. Of course, the end products of these two objectives are completely different, but practically for me it is just the same; it's a continuum.

ER: Do you have difficulties attracting good MDs and PhDs?

AF: The people who apply to work in my lab know that we are working on medical questions. Actually I am amazed at how many PhDs with no medical background want to do such research. Sometimes they have an even stronger interest than MDs in thinking about what might be helpful for patients. It's amazing to see how quickly they acquire what they need to know in terms of medical background for their research. This is not the classical way of doing research, as it is a mixture of basic and applied. Some of the people who are appointed to the hospital do lab work. For instance, there is one outstanding scientist, Geneviève de Saint Basile, who has made many beautiful contributions to the field of cytotoxic T-cells, and who is also involved in the genetic diagnosis of a number of disorders of the immune system.

ER: How did you become involved in the field of molecular medicine?

AF: By becoming an MD and through my PhD in immunology. In terms of our team we had the chance to recruit good doctors, good scientists and people who are good at both. What we would like to do is to have one foot in the ward and another in the lab. In terms of practical organization, this is of course fairly demanding. The patients with rare genetic disorders of the immune system need to be recognized and you need a lab in a place with a good research background. We have both faculties at the Necker Hospital, which has a strong scientific record in genetics and immunology.

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ER: How would you promote research in this direction?

AF: Education and funding go together. We need to attract more young people to do MD/PhD programmes and make their lives easier, especially for women. One should support them not only financially, but also otherwise. We should also attract young people who are excellent physicists or mathematicians to biological projects with medical questions. Even if they do not work directly on medical problems, we need to promote interactions. This means allowing people to go into the laboratory at a much younger age than is at least the case for medical students in France.

> **I think it is very important that young people work at the frontier between medicine and basic research**

ER: What benefits and drawbacks have you seen from your experience in the field of primary immunodeficiencies?

AF: Medical research is a sum of hopes, successes and very many drawbacks. It is like other fields of research, except that medical research includes the human element. This can be fantastic but sometimes very delicate, and we should be even more careful in handling the ethical aspects than in basic research. I think it is very important that young people work at the frontier between medicine and basic research. If their research goes back to benefit patients this is great, but even if not, it is still important. In the lab, there is a huge variety of possible combinations between research and clinical work. We have developed a clinical research programme on immunodeficiencies to describe the diseases better. For us, it's a combination that changes all the time.

Personally, I have enjoyed this very much because it gives me both a scientific and a human view on the problem. I would strongly encourage MDs to go into research even if it takes a long time to get the right training. Sometimes you suffer because the MDs consider you as a PhD and the PhDs consider you as a MD. You are a foreigner everywhere. You have to be tough, but in the end it is rewarding.

The interview was conducted by Fabian Filipp.

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